Notice of Allowability	Application No.	Applicant(s)	
	09/723,000	GORONZY ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *July 23, 2004*.

2. ☒ The allowed claim(s) is/are *48-56 and 60*.

3. ☒ The drawings filed on *09 September 2003* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Patrick Finn on September 29, 2004.

The application has been amended as follows:

IN THE CLAIMS:

Claims 57, 61 and 62 have been cancelled.

Claim 48 has been amended as follows:

48. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) comparing the frequency of $CD4^{+}/CD28^{null}$ cells in said patient to a reference frequency to obtain information about said rheumatoid arthritis condition, and

b) determining if said patient is predisposed to develop severe disease based on said information and the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele;

wherein said severe disease comprises subcutaneous nodule formation or extra-articular involvement.

Claim 60 has been amended as follows:

60. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) determining the frequency of $CD4^{+}/CD28^{null}$ cells in said patient,

b) determining the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele,

c) comparing said frequency of $CD4^{+}/CD28^{null}$ cells to a reference frequency to obtain information about said rheumatoid arthritis condition, and

d) determining if said patient is predisposed to develop severe disease based on said information and said presence or absence of said HLA-DRB1 allele;

wherein said severe disease comprises subcutaneous nodule formation or extra-articular involvement.

Examiner's Comments

2. Claims 57, 61 and 62 were cancelled. Applicant indicated that the cancellation of claims is made without prejudice. The amendments to claims 48 and 60 were made in order to clarify the meaning of "severe disease". "Severe disease" is a severe form of rheumatoid arthritis, marked by subcutaneous nodule formation and/or extra-articular involvement (specification, page 3, lines 2-4).

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance:

Applicant's appeal brief, filed July 23, 2004 is acknowledged. The arguments contained in the brief, regarding the rejection of claims 48-57 (claim 57 is now cancelled) and 60 under 35 U.S.C. 103(a) as obvious over Goronzy *et al.* (*J. Clin. Investigation*, 1994, 94:2068-2076) in view of Abril *et al.* (*Arthritis Rheum.* 1998, 40:762), had been presented in previous responses. However, upon further consideration, the arguments were found persuasive. There is no motivation in the art of record to combine the teachings of Goronzy *et al.* with Abril *et al.* As evidence that there is no motivation to combine the two references, Applicant points to the Chapman *et al.* reference (*J. Immunol.* 1996, 157:4771-4780) which discloses that frequency of $CD4^{+}/CD28^{null}$ cells and the presence/absence of HLA-DRB alleles are associated. Applicant argues that one would not have been motivated to combine Goronzy *et al.* with Abril *et al.*, which measure both factors (frequency of $CD4^{+}/CD28^{null}$ cells and the presence/absence of HLA-DRB alleles), because Chapman *et al.* teaches that the presence of one of the factors necessarily leads to the other, and therefore the measurement of both factors is not required. Lacking motivation to combine the two reference's teachings, one would not have arrived at the invention claimed in claims 48-57 (claim 57 is now cancelled) and 60.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. Claims 48-56 and 60 are allowable.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
September 30, 2004

JAMES HOUSEL 10/1/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

09/723,000 Pending claims w/ Examiner's Amdt. 9/30/2004 SBC

48. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) comparing the frequency of $CD4^+/CD28^{null}$ cells in said patient to a reference frequency to obtain information about said rheumatoid arthritis condition, and

b) determining if said patient is predisposed to develop severe disease based on said information and the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele;

wherein said severe disease comprises subcutaneous nodule formation or extra-articular involvement.

49. The method of claim 48, wherein said frequency of $CD4^+/CD28^{null}$ cells comprises the percent of $CD4^+$ cells that are CD28 negative.

50. The method of claim 48, wherein said reference frequency is derived from the $CD4^+/CD28^{null}$ cell frequency from a population.

51. The method of claim 50, wherein said population comprises a population of patients having a diffuse rheumatoid arthritis condition.

52. The method of claim 50, wherein said population comprises a population of patients having a follicular rheumatoid arthritis condition.

53. The method of claim 50, wherein said population comprises a population of patients having a granulomatous rheumatoid arthritis condition.

54. The method of claim 50, wherein said population comprises a population of healthy individuals.

55. The method of claim 50, wherein said population comprises a population of patients having subcutaneous nodules.

56. The method of claim 50, wherein said population comprises a population of patients having extra-articular involvement.

60. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) determining the frequency of $CD4^+/CD28^{null}$ cells in said patient,

b) determining the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele,

c) comparing said frequency of $CD4^+/CD28^{null}$ cells to a reference frequency to obtain information about said rheumatoid arthritis condition, and

d) determining if said patient is predisposed to develop severe disease based on said information and said presence or absence of said HLA-DRB1 allele;

wherein said severe disease comprises subcutaneous nodule formation or extra-articular involvement.